COVID-19

The association between stroke and COVID-19-related mortality: a systematic review and meta-analysis based on adjusted effect estimates

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Abstract

Objective To investigate the association between stroke and the risk for mortality among coronavirus disease 2019 (COVID-19) patients.

Methods We performed systematic searches through electronic databases including PubMed, Embase, Scopus, and Web of Science to identify potential articles reporting adjusted effect estimates on the association of stroke with COVID-19-related mortality. To estimate pooled effects, the random-effects model was applied. Subgroup analyses and meta-regression were performed to explore the possible sources of heterogeneity. The stability of the results was assessed by sensitivity analysis. Publication bias was evaluated by Begg's test and Egger's test.

Results This meta-analysis included 47 studies involving 7,267,055 patients. The stroke was associated with higher COVID-19 mortality (pooled effect = 1.30, 95% confidence interval (CI): 1.16–1.44; $I^2 = 89\%$, $P < 0.01$; random-effects model). Subgroup analyses yielded consistent results among area, age, proportion of males, setting, cases, effect type, and proportion of severe COVID-19 cases. Statistical heterogeneity might result from the different effect type according to the meta-regression ($P = 0.0105$). Sensitivity analysis suggested that our results were stable and robust. Both Begg's test and Egger's test indicated that potential publication bias did not exist.

Conclusion Stroke was independently associated with a significantly increased risk for mortality in COVID-19 patients.

Keywords COVID-19 · Stroke · Mortality · Adjusted effect estimates · Meta-analysis

Introduction

A series of studies have explored the relationship between comorbid stroke and the risk of mortality in coronavirus disease 2019 (COVID-19), but the conclusions were inconsistent or conflicting. Two previous meta-analyses on the basis of un-adjusted effect estimates failed to observe that comorbid stroke was significantly related to an increased risk of mortality in COVID-19 patients [1, 2]. To our knowledge, several risk factors including age, gender, and other underlying conditions (diabetes, hypertension, chronic kidney disease, and chronic obstructive pulmonary disease and others) have been reported to have a significant impact on the clinical progression of patients with COVID-19 [3–8]. This meant that these factors might affect the association between stroke and COVID-19 mortality. For example, the results of univariate analysis in Muhammad et al.'s study [9] showed that stroke was a risk factor for the mortality of COVID-19 (odds ratio (OR) = 2.73, 95% confidence interval (CI): 1.08–6.88), while the results of multivariate analysis demonstrated that stroke was not significantly associated with COVID-19 mortality (adjusted OR = 1.34,

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Fig. 1 Flow chart of the process of study selection
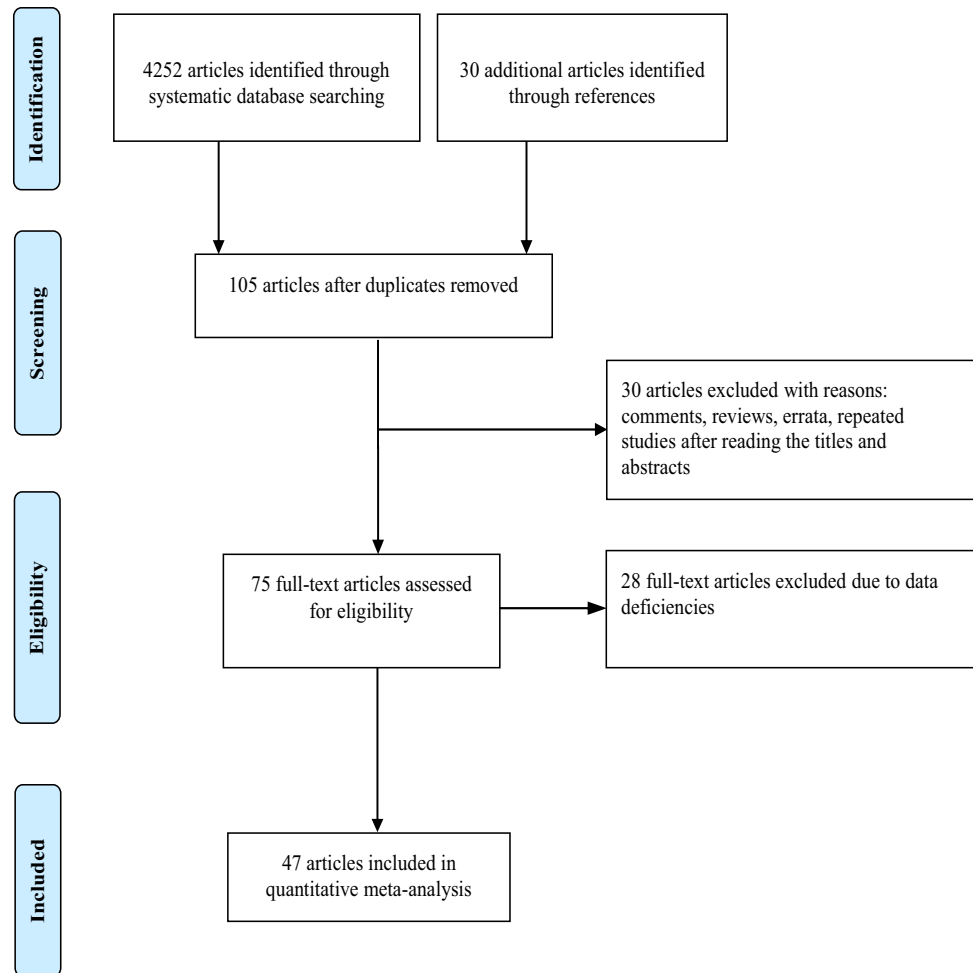
95% CI: 0.45–4.02). Similar findings were also observed by Lee et al. [10]. Therefore, a meta-analysis based on adjusted effect estimates was performed to investigate the association of stroke with fatal outcome in COVID-19 patients.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist was used to improve the reporting of this meta-analysis. Databases including PubMed, Web of Science, Scopus, and Embase were searched up to November 22, 2021, to find the relevant studies. The following search terms were used: ("COVID-19" OR "coronavirus disease 2019" OR "SARS-CoV-2" OR "novel coronavirus" OR "2019-nCoV") AND ("stroke" OR "strokes" OR "cerebral stroke" OR "acute cerebrovascular accident" OR "cerebral infarction") AND ("mortality" OR "death" OR "fatality" OR "deceased" OR

"non-survivor"). Moreover, to find more grey literature on this topic, relevant references of the included studies were also taken into account.

The following inclusion criteria were defined for the selection of the papers: (1) articles should be published in English; (2) COVID-19 patients were diagnosed according to the World Health Organization (WHO) standards; (3) articles reported adjusted effect estimates on the association between stroke and the risk of mortality among COVID-19 patients. Repeated articles, case reports, reviews, comments, protocols, errata, and articles without sufficient information were excluded. Only the articles with the most complete data could be included if studies were based on the same data sources.

Two authors selected eligible studies independently and screened the titles and abstracts on the basis of the inclusion criteria. Any disagreement would be resolved through discussion. The primary message included the following data: author, country, cohort type, cases, numbers

Table 1 Characteristics of the eligible studies included in this meta-analysis

Author	Country	Cohort type	Cases (n)	No. of stroke (%)	Age (years)	Severe COVID-19 (%)	Male (%)	Setting	Adjusted-effect (95% CI)
Atkins JL	UK	Retrospective	507	23 (4.5)	74.3 ± 4.5	NA	NA	Hospitalized	OR = 1.16 (0.75–1.81)
Perez-Guzman PN	UK	Retrospective	614	NA	69 ± 25	13.03	62.21	Hospitalized	OR = 0.89 (0.48–1.65)
Kummer BR	USA	Retrospective	3,248	387 (11.9)	67.0 ± 16.2	NA	85.19	Hospitalized	OR = 1.28 (1.01–1.63)
Gupta A	USA	Retrospective	1,296	135 (10.4)	69.8 ± 13.9	22.22	56.48	Hospitalized	OR = 1.177 (0.821–1.688)
Nimkar A	USA	Retrospective	327	91 (27.8)	71 (59–82)	NA	55.7	Hospitalized	OR = 1.1 (0.6–1.9)
Reilev M	Denmark	Retrospective	11,122	542 (4.9)	48 (33–62)	2.82	42	Hospitalized	OR = 1.4 (1.1–1.8)
Miller J	USA	Retrospective	3,633	1,758 (51.8)	58.4 ± 18.1	NA	46.2	All patients	OR = 0.94 (0.71–1.24)
Graziani D	Spain	Retrospective	793	27 (3.4)	75 ± 12	NA	83	All patients	OR = 0.76 (0.58–1.71)
Clift AK*	UK	Prospective	6,083,102	129,699 (2.13)	48.2 ± 18.6	NA	49.9	All patients	HR = 1.28 (1.19–1.39)
Liu J	China	Retrospective	774	43 (5.6)	64 (54–73)	100	58.4	Hospitalized	HR = 0.99 (0.58–1.7)
Sheshah E	Saudi Arabia	Retrospective	300	5 (1.7)	49.7 ± 13.2	7.0	86.3	Hospitalized	OR = 1.5 (0.2–10.8)
Rossi L	Italy	Retrospective	590	21 (3.6)	76.2 (68.2–82.6)	14.24	67.6	All patients	HR = 1.721 (0.985–3.008)
FAI2R**	France	Retrospective	694	25 (3.7)	55.9	12.54	33.4	All patients	OR = 1.52 (0.51–4.56)
Alguwaihes AM	Saudi Arabia	Retrospective	439	17 (3.9)	55 (19–101)	28.02	68.3	Hospitalized	HR = 1.3 (0.5–3.8)
Ling SF	UK	Retrospective	444	40 (9.0)	74 (63–83)	7.6	55.2	Hospitalized	OR = 1.09 (0.54–2.19)
Hobbs ALV	USA	Retrospective	502	57 (11.4)	62 (49–71)	35.66	55.2	Hospitalized	OR = 1.25 (0.55–2.72)
Ahlstrom B	Sweden	Retrospective	1,981	59 (3.0)	61 (52–69)	100	74	Hospitalized	HR = 1.04 (0.75–1.44)
Eskandar EN	USA	Retrospective	4,711	27 (2.4)	63.4	NA	53.3	Hospitalized	HR = 1.75 (1.4–2.1)
Muhammad R	USA	Retrospective	200	22 (11.0)	58.9 ± 15.1	35.5	60.5	Hospitalized	OR = 1.34 (0.45–4.02)
Kvale R	Norway	Retrospective	8,809	125 (1.4)	NA	NA	49.5	All patients	OR = 1.5 (1.1–2.2)
Gonzalez-Fajardo JA	Spain	Prospective	106	15 (14.15)	65.66 ± 15.49	8.87	67.92	Hospitalized	HR = 8.812 (2.25–34.516)
Efros O	Israel	Retrospective	320	29 (9.06)	63.66 ± 16.87	NA	64.06	Hospitalized	HR = 1.90 (0.83–4.32)
Aoun M	Lebanon	Retrospective	231	14 (6.1)	61.46 ± 13.99	19.91	55.4	Hospitalized	OR = 2.71 (0.89–8.28)
Caro-Codon J	Spain	Retrospective	918	41 (4.5)	63.2 ± 15.5	16.9	60.1	Hospitalized	HR = 1.61 (0.89–2.9)
Galvez-Barron C	Spain	Retrospective	103	13 (12.6)	86.75 ± 4.65	57.28	40.8	Hospitalized	OR = 0.85 (0.26–2.91)
Alwafi H	Saudi Arabia	Retrospective	706	88 (12.5)	48.0 ± 15.6	35.98	68.5	Hospitalized	OR = 0.25 (0.06–1.01)

Table 1 (continued)

Author	Country	Cohort type	Cases (n)	No. of stroke (%)	Age (years)	Severe COVID-19 (%)	Male (%)	Setting	Adjusted-effect (95% CI)
Fan FSY	China	Retrospective	3,164	NA	NA	NA	NA	Hospitalized	HR = 2.31 (1.35–3.96)
Cummins L	UK	Retrospective	1,781	138 (7.7)	59.77	8.53	55.2	Hospitalized	OR = 1.93 (1.29–2.88)
Vogels Y	Netherlands	Retrospective	114	7 (6.1)	68.0 (59.0–73.3)	100	76.3	Hospitalized	HR = 1.82 (0.62–5.33)
Azarkar Z	Iran	Retrospective	364	13(3.57)	54.28 ± 18.81	18.13	56.9	Hospitalized	OR = 5.56 (1.5–21.3)
Kelly JD	USA	Retrospective	27,640	757 (2.7)	57.59	NA	88.6	All patients	OR = 0.98 (0.75–1.29)
Panagides V	France	Retrospective	2,806	249 (8.98)	66.4 ± 16.9	12.94	57.6	Hospitalized	HR = 0.92 (0.67–1.26)
Lugon JR	Brazil	Retrospective	741	26 (3.5)	57 ± 16	28.48	61	All patients	HR = 1.37 (0.67–2.82)
Bonnet G	France	Retrospective	28,778	253 (8.9)	66.6 ± 17.0	0	57.9	Hospitalized	HR = 1.96 (1.47–2.62)
Semenzato L	France	Retrospective	87,809	5,620 (6.4)	67 ± 19	NA	53.3	Hospitalized	HR = 1.39 (1.32–1.47)
Chai C	China	Ambispective	166	4 (2.4)	65 (59–70)	NA	49	Hospitalized	HR = 3.7 (1.1–12.9)
Işık F	Turkey	Retrospective	1,897	80 (4.2)	62 (50–72)	25.83	52.7	Hospitalized	OR = 1.23 (0.608–2.486)
Bushman D	USA	Retrospective	1,029	50 (4.9)	56 (23–64)	32.8	65.5	Hospitalized	OR = 1.43 (0.78–2.62)
Bandera A	Italy	Retrospective	1,018	NA	65 ± 16	NA	NA	Hospitalized	OR = 1.15 (0.6–2.19)
Lee JH	Korea	Retrospective	7,162	200 (2.79)	47.7 ± 18.7	11.45	40.1	All patients	OR = 0.894 (0.634–1.262)
Zerbo O	USA	Retrospective	219,001	1,125 (0.5)	37.45	1.1	47.3	All patients	HR = 1.59 (1.29–1.97)
Wang B	USA	Retrospective	16,504	2,301 (13.9)	67.6 ± 12.0	17.89	47.7	All patients	HR = 1.06 (0.96–1.18)
Zagidullin NS	Russia	Retrospective	386	4 (1.04)	59 (49–66)	12.5	40.16	Hospitalized	OR = 1.09 (0.55–2.18)
Puebla Neira DA	USA	Retrospective	31,526	9,308 (29.52)	66.23 ± 12.27	23.2	53.36	Hospitalized	OR = 1.12 (1.01–1.21)
Lu Y	USA	Retrospective	608,251	10,949 (1.8)	83	2.46	32.7	All patients	HR = 0.94 (0.87–1.01)
Marques M	Spain	Retrospective	2,112	132 (6.3)	66.6 ± 17.4	16.29	42.9	Hospitalized	OR = 0.8 (0.51–1.24)
Ouattara E	France	Retrospective	98,336	6,192 (6.3)	71 (56–83)	26.19	53.8	All patients	HR = 2.91 (2.62–3.23)

* indicates combined effects based on subgroups; ** published by FAI2R /SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors; The age (years) was presented as mean ± standard deviation or median (interquartile range, IQR); *COVID-19*, coronavirus disease 2019; *CI*, confidence interval; *NA*, not available; *OR*, odds radio; *HR*, hazard radio; *USA*, the United States of America; *UK*, the United Kingdom

of stroke, mean or median age, proportion of males, setting, proportion of severe COVID-19 cases, adjusted effect estimate, and 95% CI.

Meta-analysis was performed using the R statistical software (Version 4.1.1, The R Foundation, Vienna, Austria) with "meta" package (Version 4.19-0) to calculate the pooled effect and 95% CI on the association between
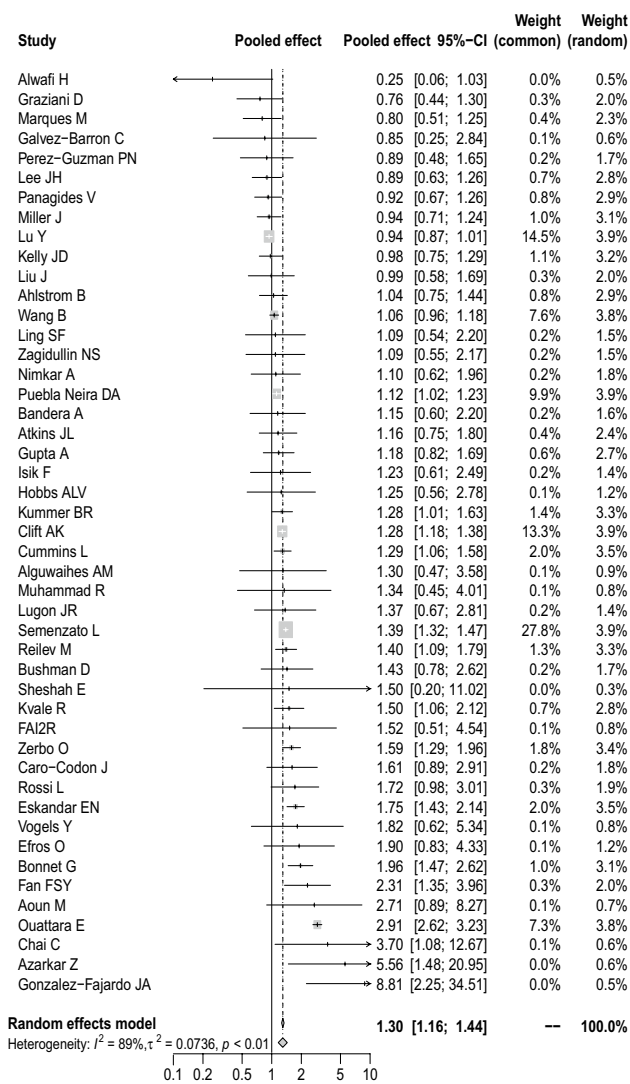
Study	Pooled effect	Pooled effect 95%-CI	Weight (common)	Weight (random)
Alwafi H		0.25 [0.06; 1.03]	0.0%	0.5%
Graziani D		0.76 [0.44; 1.30]	0.3%	2.0%
Marques M		0.80 [0.51; 1.25]	0.4%	2.3%
Galvez−Barron C		0.85 [0.25; 2.84]	0.1%	0.6%
Perez−Guzman PN		0.89 [0.48; 1.65]	0.2%	1.7%
Lee JH		0.89 [0.63; 1.26]	0.7%	2.8%
Panagides V		0.92 [0.67; 1.26]	0.8%	2.9%
Miller J		0.94 [0.71; 1.24]	1.0%	3.1%
Lu Y		0.94 [0.87; 1.01]	14.5%	3.9%
Kelly JD		0.98 [0.75; 1.29]	1.1%	3.2%
Liu J		0.99 [0.58; 1.69]	0.3%	2.0%
Ahlstrom B		1.04 [0.75; 1.44]	0.8%	2.9%
Wang B		1.06 [0.96; 1.18]	7.6%	3.8%
Ling SF		1.09 [0.54; 2.20]	0.2%	1.5%
Zagidullin NS		1.09 [0.55; 2.17]	0.2%	1.5%
Nimkar A		1.10 [0.62; 1.96]	0.2%	1.8%
Puebla Neira DA		1.12 [1.02; 1.23]	9.9%	3.9%
Bandera A		1.15 [0.60; 2.20]	0.2%	1.6%
Atkins JL		1.16 [0.75; 1.80]	0.4%	2.4%
Gupta A		1.18 [0.82; 1.69]	0.6%	2.7%
Isik F		1.23 [0.61; 2.49]	0.2%	1.4%
Hobbs ALV		1.25 [0.56; 2.78]	0.1%	1.2%
Kummer BR		1.28 [1.01; 1.63]	1.4%	3.3%
Clift AK		1.28 [1.18; 1.38]	13.3%	3.9%
Cummins L		1.29 [1.06; 1.58]	2.0%	3.5%
Alguwaihes AM		1.30 [0.47; 3.58]	0.1%	0.9%
Muhammad R		1.34 [0.45; 4.01]	0.1%	0.8%
Lugon JR		1.37 [0.67; 2.81]	0.2%	1.4%
Semenzato L		1.39 [1.32; 1.47]	27.8%	3.9%
Reilev M		1.40 [1.09; 1.79]	1.3%	3.3%
Bushman D		1.43 [0.78; 2.62]	0.2%	1.7%
Sheshah E		1.50 [0.20; 11.02]	0.0%	0.3%
Kvale R		1.50 [1.06; 2.12]	0.7%	2.8%
FAI2R		1.52 [0.51; 4.54]	0.1%	0.8%
Zerbo O		1.59 [1.29; 1.96]	1.8%	3.4%
Caro−Codon J		1.61 [0.89; 2.91]	0.2%	1.8%
Rossi L		1.72 [0.98; 3.01]	0.3%	1.9%
Eskandar EN		1.75 [1.43; 2.14]	2.0%	3.5%
Vogels Y		1.82 [0.62; 5.34]	0.1%	0.8%
Efros O		1.90 [0.83; 4.33]	0.1%	1.2%
Bonnet G		1.96 [1.47; 2.62]	1.0%	3.1%
Fan FSY		2.31 [1.35; 3.96]	0.3%	2.0%
Aoun M		2.71 [0.89; 8.27]	0.1%	0.7%
Ouattara E		2.91 [2.62; 3.23]	7.3%	3.8%
Chai C		3.70 [1.08; 12.67]	0.1%	0.6%
Azarkar Z		5.56 [1.48; 20.95]	0.0%	0.6%
Gonzalez−Fajardo JA		8.81 [2.25; 34.51]	0.0%	0.5%
Random effects model		**1.30 [1.16; 1.44]**	**--**	**100.0%**

Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.0736$, $p < 0.01$

0.1 0.2 0.5 1 2 5 10

Fig. 2 Forest plot on the association of stroke with mortality of COVID-19 patients

stroke and COVID-19 mortality. The I^2 statistic was used to assess heterogeneity, which was considered significant if $I^2 > 50\%$. A random-effects model was adopted if heterogeneity was significant; otherwise, a fixed-effects model would be implemented. Subgroup analyses were conducted according to the area, age, cohort type, effect type, setting, cases, proportion of severe COVID-19 cases, and the proportion of males to explore the sources of heterogeneity. The robustness of the results was tested using sensitivity analysis by eliminating data one at a time. The authors also used the Begg's and Egger's tests to detect publication

bias. Statistically significant difference was considered when P value was less than 0.05.

Results

The literature search identified 4252 articles through database mining. A total of 4177 of them were excluded after screening the titles and abstracts, and 75 reports were reviewed for full-text evaluation. As a result, we included 47 studies of 7,267,055 patients [9–55]. A flowchart of the study search and selection was shown in Fig. 1. Basic characteristics of the included studies were presented in Table 1.

Overall, comorbid stroke was significantly linked to an increased risk of mortality in patients with COVID-19 (pooled effect = 1.30, 95% CI: 1.16–1.44, random-effects model, Fig. 2). This significant association was also observed in the subgroup analyses based on cases (23 studies, pooled effect = 1.27, 95% CI: 1.08–1.48 for < 1000 cases; 24 studies, pooled effect = 1.29, 95% CI: 1.13–1.46 for ≥ 1000 cases), mean age (16 studies, pooled effect = 1.26, 95% CI: 1.19–1.34 for < 60 years old; 29 studies, pooled effect = 1.30, 95% CI: 1.13–1.51 for ≥ 60 years old), proportion of males (13 studies, pooled effect = 1.16, 95% CI: 1.00–1.33 for < 50%; 31 studies, pooled effect = 1.36, 95% CI: 1.18–1.57 for ≥ 50%), setting (34 studies, pooled effect = 1.31, 95% CI: 1.18–1.45 for hospitalized patients; 13 studies, pooled effect = 1.25, 95% CI: 1.01–1.56 for all patients), area (11 studies, pooled effect = 1.48, 95% CI: 1.01–2.18 for Asia; 22 studies, pooled effect = 1.34, 95% CI: 1.14–1.58 for Europe; 14 studies, pooled effect = 1.18, 95% CI: 1.04–1.35 for Americas), effect estimates (20 studies, pooled hazard ratio (HR) = 1.51, 95% CI: 1.26–1.80; 27 studies, pooled OR = 1.14, 95% CI: 1.07–1.21), and proportion of severe COVID-19 cases (13 studies, pooled effect = 1.25, 95% CI: 1.03–1.51 for < 14%; 20 studies, pooled effect = 1.32, 95% CI: 1.08–1.62 for ≥ 14%) (Table 2). As we implemented subgroup analysis by cohort type, the association was still significant in the subgroups of retrospective studies (44 studies, pooled effect = 1.27, 95% CI: 1.14–1.42) and ambispective study (1 study, pooled effect = 3.70, 95% CI: 1.08–12.67), while no significant association was found in the subgroup of prospective studies (2 studies, pooled effect = 2.96, 95% CI: 0.45–19.31) (Table 2).

And the outputs of meta-regression demonstrated that effect type might be the source of heterogeneity ($P = 0.0105$) (Table 2). Sensitivity analysis by omitting each eligible study one by one demonstrated that our findings were stable and robust (Fig. 3). Publication bias was not found in the Begg's test ($P = 0.0864$) and Egger's test ($P = 0.8776$) (Fig. 4).

Table 2 Subgroup analysis and meta-regression

Variables	No. of studies	Meta-regression			Subgroup analysis	Heterogeneity		
		Tau^2	z value	P value	Pooled ES (95% CI)	I^2	Tau^2	P value
Cases	-	0.0759	−0.2204	0.8255	-	-	-	-
< 1000	23	-	-	-	1.27 (1.08–1.48)	32%	0.0126	0.07
≥ 1000	24	-	-	-	1.29 (1.13–1.46)	94%	0.0825	< 0.01
Age (years)	-	0.0743	-	0.3530	-	-	-	-
< 60	16	-	-	-	1.26 (1.19–1.34)	45%	0.0217	0.03
≥ 60	29	-	0.5354	0.5924	1.30 (1.13–1.51)	93%	0.0948	< 0.01
NA	2	-	1.4386	0.1503	1.70 (1.27–2.28)	43%	0.0399	0.19
Male (%)	-	0.0714	-	0.3402	-	-	-	-
< 50	13	-	-	-	1.16 (1.00–1.33)	80%	0.0356	< 0.01
≥ 50	31	-	1.3648	0.1723	1.36 (1.18–1.57)	89%	0.0882	< 0.01
NA	3	-	0.9429	0.3457	1.44 (1.06–1.94)	54%	0.0874	0.11
Area	-	0.0743	-	0.4816	-	-	-	-
Asia	11	-	0.9885	0.3229	1.48 (1.01–2.18)	60%	0.2077	< 0.01
Europe	22	-	1.0192	0.3081	1.34 (1.14–1.58)	91%	0.0964	< 0.01
America	14	-	-	-	1.18 (1.04–1.35)	76%	0.0340	< 0.01
Cohort type	-	0.0780	-	0.2055	-	-	-	-
Retrospective	44	-	−1.5469	0.1219	1.27 (1.14–1.42)	89%	0.0736	< 0.01
Prospective	2	-	−1.1170	0.2640	2.96 (0.45–19.31)	87%	1.6176	< 0.01
Ambispective	1	-	-	-	3.70 (1.08–12.67)	-	-	-
Effect	-	0.0645	−2.5578	0.0105	-	-	-	-
HR	20	-	-	-	1.51 (1.26–1.80)	95%	0.1112	< 0.01
OR	27	-	-	-	1.14 (1.07–1.21)	17%	0.0027	0.21
Setting	-	0.0766	0.4118	0.6805	-	-	-	-
Hospitalized	34	-	-	-	1.31 (1.18–1.45)	56%	0.0290	< 0.01
All patients	13	-	-	-	1.25 (1.01–1.56)	96%	0.1257	< 0.01
Severe COVID-19 (%)	-	0.0782	-	0.9113	-	-	-	-
< 14	13	-	-	-	1.25 (1.03–1.51)	81%	0.0663	< 0.01
≥ 14	20	-	0.4223	0.6728	1.32 (1.08–1.62)	93%	0.1140	< 0.01
NA	14	-	0.3038	0.7613	1.30 (1.13–1.49)	62%	0.0326	< 0.01

ES, effect sizes; *CI*, confidence interval; *NA*, not available; *OR*, odds radio; *HR*, hazard radio; *COVID-19*, coronavirus disease 2019

Discussion

Two previous meta-analyses did not observe the significant relationship between comorbid stroke and the increased risk of mortality in COVID-19 patients on the basis of un-adjusted effect estimates [1, 2]. In order to exclude the influence of factors such as gender, age, and comorbidities, we conducted a meta-analysis of 47 articles involving 7,267,055 patients that contained the results of multivariate analysis. The results showed that comorbid stroke was significantly associated with an increased risk of mortality in COVID-19 patients on the basis of confounders-adjusted effect estimates, which demonstrated that stroke might be an independent risk factor for COVID-19-related mortality. The outputs of subgroup analyses stratified by age, proportion of male patients, area, cases, setting, effect type, and proportion of severe COVID-19 infection were in consistence with the conclusion above. According to the results of meta-regression, heterogeneity may originate from the different effect indicators used in the included studies.

Stroke has been confirmed increasing the risk of pulmonary complications like pneumonia, which could lead to the fatal outcome of COVID-19 patients
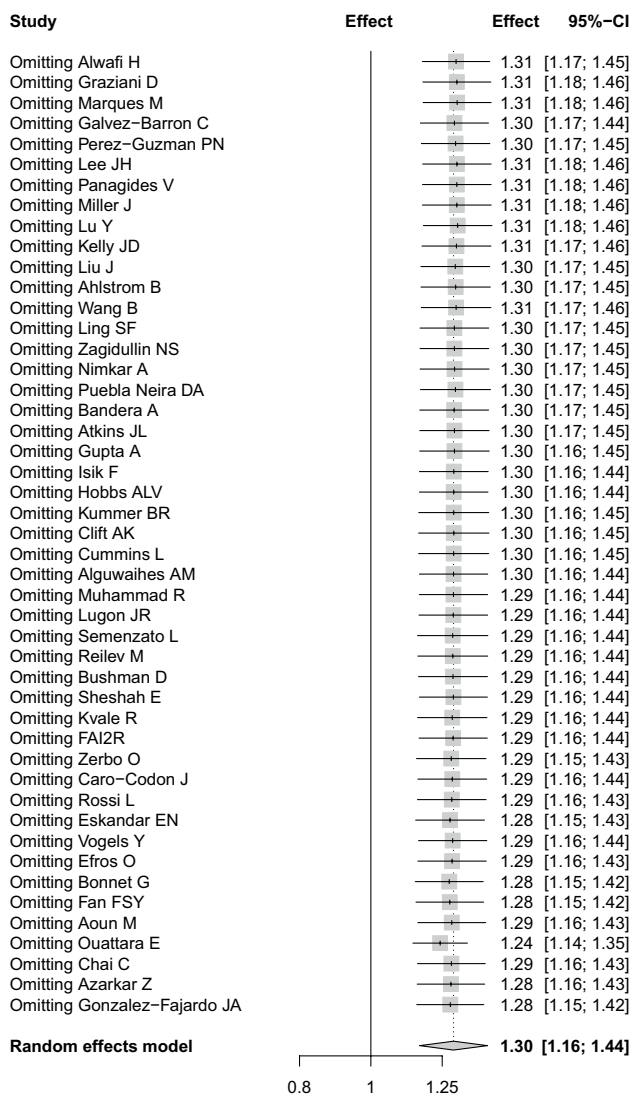
Study	Effect	Effect	95%−CI
Omitting Alwafi H		1.31	[1.17; 1.45]
Omitting Graziani D		1.31	[1.18; 1.46]
Omitting Marques M		1.31	[1.18; 1.46]
Omitting Galvez−Barron C		1.30	[1.17; 1.44]
Omitting Perez−Guzman PN		1.30	[1.17; 1.45]
Omitting Lee JH		1.31	[1.18; 1.46]
Omitting Panagides V		1.31	[1.18; 1.46]
Omitting Miller J		1.31	[1.18; 1.46]
Omitting Lu Y		1.31	[1.18; 1.46]
Omitting Kelly JD		1.31	[1.17; 1.46]
Omitting Liu J		1.30	[1.17; 1.45]
Omitting Ahlstrom B		1.30	[1.17; 1.45]
Omitting Wang B		1.31	[1.17; 1.46]
Omitting Ling SF		1.30	[1.17; 1.45]
Omitting Zagidullin NS		1.30	[1.17; 1.45]
Omitting Nimkar A		1.30	[1.17; 1.45]
Omitting Puebla Neira DA		1.30	[1.17; 1.45]
Omitting Bandera A		1.30	[1.17; 1.45]
Omitting Atkins JL		1.30	[1.17; 1.45]
Omitting Gupta A		1.30	[1.16; 1.45]
Omitting Isik F		1.30	[1.16; 1.44]
Omitting Hobbs ALV		1.30	[1.16; 1.44]
Omitting Kummer BR		1.30	[1.16; 1.45]
Omitting Clift AK		1.30	[1.16; 1.45]
Omitting Cummins L		1.30	[1.16; 1.45]
Omitting Alguwaihes AM		1.30	[1.16; 1.44]
Omitting Muhammad R		1.29	[1.16; 1.44]
Omitting Lugon JR		1.29	[1.16; 1.44]
Omitting Semenzato L		1.29	[1.16; 1.44]
Omitting Reilev M		1.29	[1.16; 1.44]
Omitting Bushman D		1.29	[1.16; 1.44]
Omitting Sheshah E		1.29	[1.16; 1.44]
Omitting Kvale R		1.29	[1.16; 1.44]
Omitting FAI2R		1.29	[1.16; 1.44]
Omitting Zerbo O		1.29	[1.15; 1.43]
Omitting Caro−Codon J		1.29	[1.16; 1.44]
Omitting Rossi L		1.29	[1.16; 1.43]
Omitting Eskandar EN		1.28	[1.15; 1.43]
Omitting Vogels Y		1.29	[1.16; 1.44]
Omitting Efros O		1.29	[1.16; 1.43]
Omitting Bonnet G		1.28	[1.15; 1.42]
Omitting Fan FSY		1.28	[1.15; 1.42]
Omitting Aoun M		1.29	[1.16; 1.43]
Omitting Ouattara E		1.24	[1.14; 1.35]
Omitting Chai C		1.29	[1.16; 1.43]
Omitting Azarkar Z		1.28	[1.16; 1.43]
Omitting Gonzalez−Fajardo JA		1.28	[1.15; 1.42]
Random effects model		**1.30**	**[1.16; 1.44]**

0.8   1   1.25

Fig. 3 Sensitivity analysis

[56–58]. It might partly explain why COVID-19 patients with stroke displayed a higher mortality in our analysis. From another perspective, infection was a vital risk factor for stroke, especially systemic upper respiratory disease [59, 60]. The spike protein surface unit of SARS-CoV-2 highly binds to human ACE-2 receptor, which affects the normal physiological function of the ACE-2 to degrade ANG II , causing neuronal damage and endothelial cell apoptosis [61]. The dysfunction of endothelial cell, leading to fibrinolysis inhibition and excessive thrombin production [62], plays an important role in the occurrence of thrombotic events [63]. The human immune system will produce amounts of proinflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), and IL-6 when SARA-CoV-2 infects the body [64]. This phenomenon referred to as "cytokine storm" results in the degradation of the extracellular matrix (ECM), which is responsible for maintaining the integrity and stability of vascular endothelial cells. Degradation of the ECM contributes to the extravasation of blood components, and leads to hemorrhagic brain injury [65]. Worse still, stroke patients suffering from COVID-19 were more susceptible to undesirable outcomes and greater mortality rates compared with those without [66, 67]. A higher risk of large vessel occlusion and hemorrhagic transformation among ischemic stroke patients with COVID-19, combined with COVID-19 patients being more prone to intracerebral hemorrhage, might contribute to this difference [68–70]. Previous study has shown a past history of cerebrovascular disease might be associated with an increased stroke risk in COVID-19 patients [71]. Thus, we suspected that patients with a history of stroke are more likely to trigger above-mentioned mechanisms, leading to higher mortality of COVID-19 patients with pre-existing stroke. During clinical treatment, more attention should be paid to the possible two-way relationship between stroke and COVID-19 infection.

However, several limitations should be acknowledged. First, our study was limited due to lack of explanation of how stroke was defined in the literature and therefore we could not explore the relationship between different stroke types and COVID-19 mortality. Furthermore, it needs to be acknowledged that most of the selected articles were retrospective observational studies, which were not able to completely explain the casual link between the stroke and COVID-19 mortality, implying that more prospective studies with larger samples are necessary to verify the findings. Lastly, the pooled effects were estimated based on risk factors-adjusted effects, but the adjusted risk factors were not fully consistent across the included researches.

In conclusion, our data indicated that stroke was related to a significantly increased risk for COVID-19 mortality. These findings were supposed to provide a basis for risk scales in the care of patients with COVID-19 in emergency services or intensive care units.
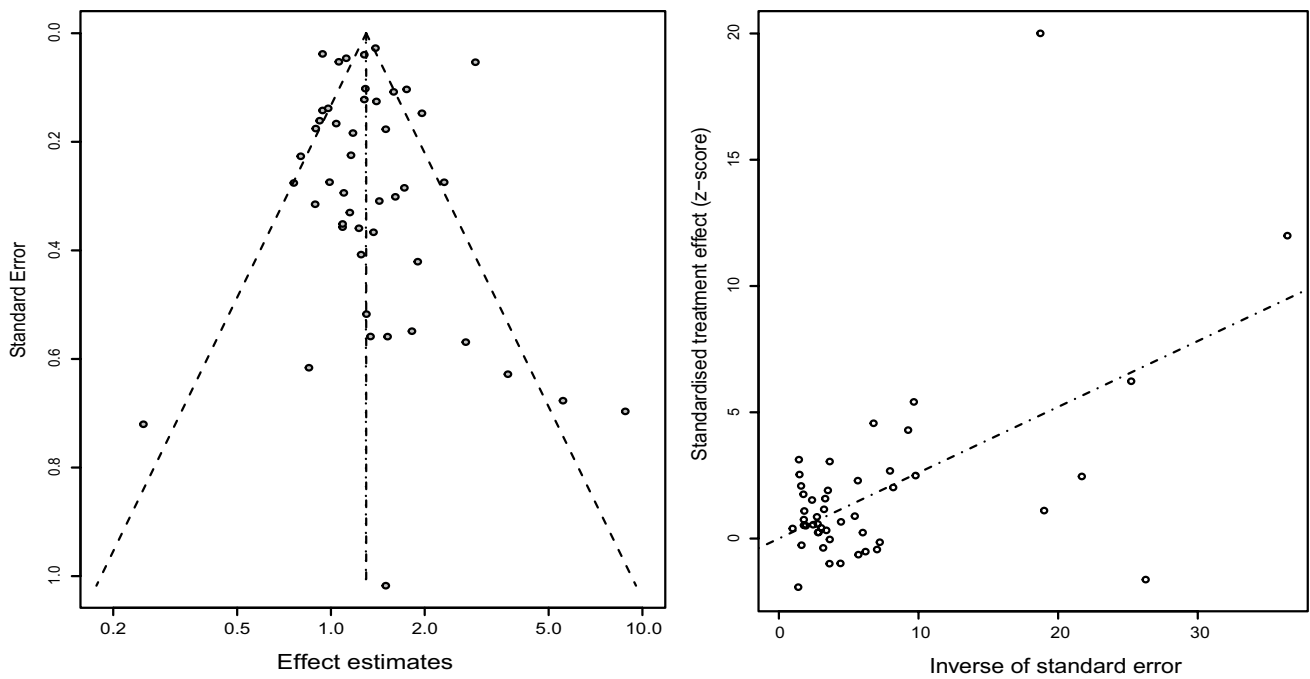
Fig. 4 Publication bias based on funnel plot and radial plot

Declarations

Ethics approval Not applicable.

Conflict of interest The authors declare no competing interests.

Informed consent Not applicable.

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